REMARKS

Claims 1-16, 19-27 and 29-33 are pending and under examination. Claims 1, 6, 7, 19, 21, 22, 23 and 30 have been amended. Claim 29 has been cancelled without prejudice as being substantially similar to claim 23. Support for the amendments can be found throughout the application as filed. In particular, support for the amendment in claims 1, 6, 19, 23 and 30, directed to a metabolic network can be found at, for example, in each claim's preamble. Support for the amendment in claims 1, 6, 19, 23 and 30, directed to logic constraints constraining a boundary for an available flux distribution to produce an altered flux balance analysis model including a kinetic, regulatory and/or expression boundary can be found at, for example, page 2, second paragraph; page 7, last paragraph through page 8, first full paragraph; page 10, second paragraph through page 11, second paragraph, in the Examples and in the word "constraint" found throughout the application. Additional exemplary support also can be found at, for example, page 11, third paragraph through the paragraph bridging pages 17 and 18, and in the paragraph bridging pages 13 and 14 therein, and in the Examples. Support for the amendment to claim 19, directed to a flux balance analysis model contained on a computer readable medium and to commands for producing an altered flux balance analysis model can be found in Figure 1 and at, for example, page 1, para. 2; page 4, Summary of the Invention, lines 4-5, and page 56, para. 2; page 58, last paragraph. Support for the amendment to claims 4, 14, 26 and 30, directed to applying mixed integer linear programming, can be found at, for example, page 25, para. 1-3; pages 26-27; page 18, para. 1; page 20, last paragraph, and in the Examples set forth at pages 27-59. Claims 7, 21 and 22 have been amended to correct obvious informalities. Claims 16 has been amended to correct an obvious informality relating to antecedent support. Accordingly, the amendments do not raise any issues of new matter and entry thereof is respectfully requested.

respectfully requested. Applicants have reviewed the Office Action mailed September 28, 2006, and respectfully all rejections for the reasons that follow.

Formalities

Claim 22 stands objected allegedly for failing to further limit the base claim from which it depends and claim 7 stands objected allegedly for containing a typographical error.

Claim 22 depends from claim 1 and references the correct preamble language of its base claim. Claim 1 recites "applying logic constraints to the flux balance analysis model to thereby tighten the boundaries for the available flux distributions." Claim 22 further limits claim 1 because it recites that the logic constraints further include DNA experimental data constraints. Accordingly, claim 22 properly depends from its base claim and withdrawal of this objection is respectfully.

Claim 21 also has been amended to reference the correct preamble language of its base claim and claim 7 has been amended to incorporate the suggested correction.

Rejections Under 35 U.S.C. § 101

Claims 1-8, 10-15, 19-27, 29-31 and 33 stand rejected under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. The Office alleges that the claimed methods fail to result in a physical transformation of matter or produce a concrete, tangible and useful result that is a practical application. In support, the Office alleges that applying constraints to a model corresponds to a mathematical manipulation and that none of the claims recite communicating a result in a tangible format such as a display of the altered model to a user. The Office concedes that claims 16 and 32, directed to engineering a change in an

organism, result in a physical transformation of matter. With respect to claim 19, the Office alleges that no physical limitations of the system are recited and therefore, concludes that system merely corresponds to data, which is nonfunctional descriptive material.

The claimed subject matter does not require computer implementation such as communicating a display to a user in order to satisfy the requirements of § 101. Applicants maintain that the claims satisfy the statutory requirements of § 101 as written. However, the claims have been amended to explicitly recite the outcome of applying logic constraints to produce an altered model having increased predictive capabilities compared to the flux balance analysis model alone. Similarly, the claimed system explicitly recites commands for producing such an altered model. The enhanced predictive capabilities result from applying logic constraints that constrain a boundary for an available flux distribution. Generating a model having enhanced predictability of an organism's cellular metabolism satisfies the statutory requirements and the Federal case law for statutory subject matter because it yields a practical application of the claimed methods and system.

Initially with respect to the system of claim 19, the claimed system for modeling cellular metabolism of an organism falls within both the Federal precedent and within the definition of a computer related structure containing functionally descriptive material as well as within the Office's Guidelines exemplifying statutorily patentable subject matter for such inventions. The claimed system imparts functionality when employed as a computer component and it contains a specified relationship such that the claimed model does not constitute nonfunctional descriptive material *per se*.

Section 101 of Title 35 provides that any new and useful invention or discovery which is a process, machine, manufacture, or composition of matter qualifies as patentable subject matter.

In holding that genetically modified bacteria was statutory subject matter, the Supreme Court in *Diamond v. Charkrabarty* concluded that Congress plainly intended a broad scope for patentable subject matter and that the enumerated categories in § 101 "include anything under the sun that is made by man." 445 U.S. 303, 308-09 (1980); *accord Diamond v. Diehr*, 450 U.S. 175, 182 (1981).

Claim 19 is directed to a system for modeling cellular metabolism of an organism which includes a flux balance analysis model containing a relationship of stoichiometric mass balances of metabolic and cellular composition information for a metabolic network, logic constraints for constraining a boundary for an available flux distribution and commands for producing an altered model with improved predictive capabilities. The plain language of claim 19 places the claimed system within the statutory categories enumerated in § 101. A system is a thing and as such is a machine, manufacture or composition of matter. *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F. 3d 1368, 1375 (Fed. Cir. 1998).

The Office's reasoning that because the system allegedly lacks physical limitations it comprises merely nonfunctional descriptive material and is precluded from statutory subject matter appears unfounded.

First, the claimed system contains a flux balance analysis model that specifies a relationship of metabolic and cellular composition information. Further, the claim now recites commands for producing an altered flux balance analysis model even though production of the altered model was apparent in the claims as written because the application of logic constrains will produce the altered model.

Second, the inquiry of whether a claimed invention is statutory patentable is whether it has a practicable application. This inquiry is relevant to systems, such as the system at issue in

State Street, which contain computer related algorithms or business methods to separate abstract ideas, laws of nature and natural phenomena from patentable subject matter. *State Street*, 149 F. 3d at1373-74 (Fed. Cir. 1998) (noting that the Freeman-Walter-Abele test for mathematical algorithm related inventions "has little, if any, applicability to determining the presence of statutory subject matter"). The system in *State Street* related to a data processing system for managing a financial services configuration. The system consisted of a series of arithmetic logic circuits configured to process financial information that can be retrieved by a user. Hence, the algorithm retrieved data, used it to calculate a result that could then be retrieved by a user. Similarly, as here, the claimed system utilizes metabolic and cellular information and logic constraints to produce a metabolic model that has improved predictive capabilities of the organisms biochemical behavior. The practical application for the system in *State Street* was the calculation of financial data into a final share price. *Id.* at 1373. Similarly, the claimed invention has the practical application of predicting cellular metabolism of an organism from the calculation of stoichiometric mass balances into flux distributions and improving the predictive capabilities of this flux balance analysis model by applying a plurality of logic constraints.

The distinction relied on by the Office that the claimed invention is merely data because it allegedly lacks a physical limitation is unsupported because the invention claims a model of an organism. The claims also now explicitly recite commands for producing the altered model. Further, the distinction relied on by the Office that the claimed system is merely nonfunctional descriptive material because it is merely data also is unfounded. Applicants discern little distinction between a system which produces an altered model for predicting an organism's capabilities using metabolic and cellular information and the system in *State Street* that produced share prices based on financial information.

Further, the Office cites to M.P.E.P. § 2106 for supporting the proposition that merely claiming nonfunctional descriptive material does not make it statutory, asserting that the claimed system constitutes nonfunctional descriptive material allegedly because it does not have a physical limitation and, therefore, constitutes merely data. This apparent reasoning fails to provide a basis for the conclusion that the claimed system containing the recited flux balance analysis model contained on a computer readable medium is nonfunctional. The mere assertion that the claimed model fails to impart functionality lacks such a basis because it is conclusory. Similarly, the mere assertion that the claimed model fails to recite a physical limitation also lacks such a basis because the physical or non-physical nature of a material has little to do with whether that material is functional. Absent a reasoning why the claimed computer readable medium or media containing the recited flux balance analysis model is considered to be nonfunctional, such broad conclusory statements fail to satisfy the Office's burden for a proper rejection under § 101.

Further, while not conceding that the Office's application of a functional descriptive test or the criteria set forth in its guidelines for computer related inventions are applicable following *State Street* to the claimed system, the assertion that the claimed invention containing the recited model predictive of an organism's cellular metabolism is nonfunctional is unfounded based on the plain language of the claim. The Office's own M.P.E.P. guidelines, which are consistent with the Office's Interim Guidelines published November 22, 2005, because the entire rationale and express language of, for example, M.P.E.P. § 2106 (IV)(B)(1) can be found set forth in Annexes II-V of the Interim Guidelines, set forth certain views regarding the patentability of functional descriptive or nonfunctional descriptive material for computer related inventions and exemplifies

a data structure stored on a computer readable medium to be patentable subject matter as functional descriptive material. M.P.E.P. § 2106 (IV)(B)(1). For example, the guidelines state:

> When functional descriptive material is recorded on some computer-readable medium it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized. Compare *In re Lowry*, 32 F.3d 1579, 1583-84, 32 USPQ2d 1031, 1035 (Fed. Cir. 1994) (claim to data structure stored on a computer readable medium that increases computer efficiency held statutory) and *Warmerdam*, 33 F.3d at 1360-61, 31 USPQ2d at 1759 (claim to computer having a specific data structure stored in memory held statutory product-by-process claim) with *Warmerdam*, 33 F.3d at 1361, 31 USPQ2d at 1760 (claim to a data structure per se held nonstatutory).

M.P.E.P. § 2106 (IV)(B)(1) (emphasis added). The guidelines further exemplify that works protected under copyright law such as music are nonfunctional descriptive material and do not become statutorily patentable merely by recording onto a compact disk. *Id.* Thus, the Office's own guidelines exemplify relationships of data, such as a data structure, to be statutory patentable subject matter when recorded on a computer readable medium.

The guidelines further define functionally descriptive and nonfunctional descriptive material to be:

> Descriptive material can be characterized as either "functional descriptive material" or "nonfunctional descriptive material." In this context, "functional descriptive material" consists of data structures and computer programs which impart functionality when employed as a computer component. (The definition of "data structure" is "a physical or logical relationship among data elements, designed to support specific data manipulation functions." The New IEEE Standard Dictionary of Electrical and Electronics Terms 308 (5th ed. 1993).) "Nonfunctional descriptive material" includes but is not limited to music, literary works and a compilation or mere arrangement of data.

Id. Thus, according to these definitions, functional descriptive material includes a relationship among data elements that imparts functionality when employed as a computer component.

The claimed system containing the recited model included on a computer readable medium falls within this definition and should be considered functional descriptive material and

statutorily patentable. For example, the system explicitly recites that it is a model contained on a computer readable medium and that it contains commands for producing an altered model. Although clear as originally written, claim 19 is explicit that the claimed system is a computer component. The claimed system also consists of a physical or logical relationship among data elements because it claims a flux balance analysis model utilizing stoichiometric mass balances of metabolic and cellular composition information. Further, the claimed system containing the recited model also imparts functionality when employed as a computer component because is used to produce a model of an organism's metabolism that has improved predictive capabilities.

In light of the above remarks, Applicants maintain that claim 19 is directed to statutory patentable subject matter which has a practical application. Applicants further maintain that claim 19 also satisfies the Offices non-binding guidelines for statutory patentable subject matter for computer related inventions. Accordingly, withdrawal of this ground of rejection is respectfully requested.

With respect to the methods for modeling cellular metabolism of an organism of claims 1-8, 10-15, 19-27, 29-31 and 33, the Office alleges that the methods of the invention do not recite communicating a result in a tangible format such as a display of the altered model to a user and concludes that the claimed methods fail to result in a physical transformation of matter or produce a concrete, tangible and useful result that is a practical application.

As above in context of the claimed system, Applicants do not concede that the Office's Interim Guidelines or the requirements set forth therein are the applicable authority for assessing statutory subject matter. Claims 1, 6, 23 and 30, and their dependents, are directed to a method for modeling cellular metabolism of an organism. The method includes, *inter alia,* constructing a flux balance analysis model using stoichiometric mass balances to identify available flux

distribution boundaries. Applying logic constraints to the model to produce an altered flux balance analysis model having improved predictive capabilities where a boundary for an available flux distribution is constrained. The result of predicting cellular metabolism of an organism from the calculation of stoichiometric mass balances into flux distributions and improving the predictive capabilities of this metabolic model by applying a plurality of logic constraints constitutes a practical application under the applicable Federal case law and under the Office's guidelines. Nevertheless, to further prosecution, Applicants set forth below an analysis showing that the claimed methods satisfy the Office's non-binding Interim Guidelines.

With respect to producing a result having a practical application, the result satisfies the Office's "useful result" criteria because it has a specific, substantial and credible utility. The utility of the claimed invention is specific to the subject matter claimed, and not general, because the claims recite that the altered flux balance analysis model that improves the predictive capabilities of an organism's metabolic network. Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility, Nov. 22, 2005, section IV.B.2.b., *citing* M.P.E.P. § 2107 (*see also* Revised Interim Utility Guidelines Training Materials at page 5 (1999)). The utility is substantial because it has a real world use, namely, improved predictive capabilities of an organism's cellular metabolism, such as for diagnostic or therapeutic purposes. *Id.* The utility also is credible because there is no reason for one skilled in the art to question the objective truth of the statement of utility and it is currently available for use. *Id.* Therefore, the claimed invention produces a useful result under the non-binding Interim Guidelines because it yields a specific, substantial and credible result.

Second, the claimed invention also satisfies the Office's "tangible result" criteria because it yields an altered flux balance analysis model having a boundary constrained for an available

flux distribution with improved predictive capabilities of an organism's cellular metabolism. The Interim Guidelines correctly acknowledge that:

> The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing.

Interim Guidelines, Nov. 22, 2005, section IV.B.2.b(2) (emphasis added); *see also In re Lundgren* cited in Applicants' previous response and discussed further below.

Therefore, in contrast to the assertions in the Office Action, there is no requirement for a claimed invention to be either tied to a particular machine or to transform a thing to a different state. The Office's own guidelines acknowledged this fact. Accordingly, any rejection based on this requirement is respectfully requested to be withdrawn.

Under this "tangible result" prong of the Office's guidelines, the requirement for a tangible result also must be differentiated from three judicial exceptions to patentability, which are: (1) laws of nature; (2) physical phenomena, and (3) abstract ideas. The guidelines further define the meaning of "tangible" to be opposite of "abstract."

With respect to the first two judicial exceptions above, the invention claims neither a law of nature or a physical phenomena *per se*. Rather, the claimed invention is directed to methods for modeling cellular metabolism of an organism. The methods include applying logic constraints to a flux balance analysis model of a metabolic network to produce an altered model having a boundary for an available flux distribution constrained to improve its predictive capabilities. There is no recitation in this claim of merely a law of nature or a physical phenomena. Accordingly, the claimed invention cannot be statutory unpatentable under these two judicial exception.

Further, there also is nothing in the claimed invention that constitutes a mere abstract idea. First, the claimed invention is more than just an idea because it claims a flux balance analysis model that utilizes stoichiometric mass balances of metabolic and cellular composition information and identifies boundaries for available flux distributions of an organism's cellular metabolism. The claimed method further applies logic constraints to constrain an available flux distribution to produce an altered metabolic model with improved capabilities. Hence, the ability to predict an organism's cellular metabolism is more than an idea. Rather, it is an actual outcome.

Second, the claimed invention also is not abstract. The term "abstract" is defined as:

> [c]onsidered apart from any application to a particular object or specific instance . . . . insufficiently factual . . . . having no reference to a thing or things -- opposed to concrete. . . . . Expressing a property, quality, attribute, or relation viewed apart from the other characteristics inhering in or constituting an object.

Webster's Third New International Dictionary, Unabridged. Merriam-Webster, 2002. http://unabridged.merriam-webster.com (21 Aug. 2006) (emphasis added).

Applicants maintained that the claimed invention is sufficiently factual because it recites a flux balance analysis model which utilizes stoichiometric mass balances of metabolic and cellular information, applies logic constraints to constrain a boundary for an available flux distribution and produces an altered metabolic model having improved predictive capabilities of an organism's metabolic network. Further, the claimed invention is not claimed apart from, or without reference to, a thing or to characteristics in an object because it specifically recites the requisite metabolic and cellular stoichiometric mass balances for a metabolic network of an organism. Accordingly, the invention is concrete and not abstract because it is sufficiently factual and does not recite purely theoretical ideas detached from a particular object. Therefore,

the claimed invention also produces a tangible result under the non-binding Interim Guidelines because it does not claim a law of nature, a physical phenomena or merely abstract idea apart from any application to a particular object.

Finally, the claimed invention also satisfies the Office's "concrete result" criteria. The Interim Guidelines define this prong as being the opposite of "concrete" which is "unrepeatable or unpredictable." Interim Guidelines, Nov. 22, 2005, section IV.B.2.b(3). Applicants respectfully point out that the invention claims producing an altered flux balance analysis model having improved predictive capabilities of an organism's cellular metabolism. Further, the application provides detailed teachings and guidance throughout for how to make and use the invention by applying logic constraints to constrain an available flux distribution to produce an altered model having improved predictive capabilities of an organism's cellular metabolism. Therefore, the claimed invention further produces a concrete result under the non-binding Interim Guidelines because it yields a result that is determinative of a systemic property of a biochemical reaction network.

Applicants also respectfully draw the Office's attention to recent authority which overrules rejections based on a requirement that an invention must interact with a computer in the execution of a method similar to the requirement that the claimed system result in a physical transformation or recite communicating a result in a tangible format such as a display of the altered model. *In re Lundgren*, B.P.A.I. Case Nos. 2003-2088 (Sept. 28, 2005) (*Per Curium*). The claimed Lundgren invention was directed to method of compensating a manager. *Id.*, slip op. at p.1. The Examiner rejected the claimed invention for being directed to non-statutory subject matter allegedly because:

> [B]oth the invention and the practical application to which it is directed to be outside the technological arts, namely an economic theory expressed as a mathematical algorithm without the disclosure or suggestion of computer, automated means, apparatus of any kind.

Id. slip op. at p.4 (emphasis added).

In re Lundgren dispelled any notion for requiring such physical interactions to exist when the court stated:

> In *Musgrave*, the court reversed a rejection under 35 U.S.C. § 101 that the claims under review therein were non-statutory because it disagreed with the Board that "these claims . . . are directed to non-statutory processes merely because some or all of the steps therein can also be carried out in or with the aid of the human mind or because it may be necessary for one performing the processes to think."

In re Lundgren, slip op. at p.7 (emphasis added, citations omitted).

Therefore, The Board of Appeals and Interferences of the U.S. Patent and Trademark Office has overturned rejections attempting to require method claims to include machine or computer processing limitations such as the instant requirement for a physical transformation or communicating a result in a tangible format. *Id.* This decision by the U.S.P.T.O. overrules any rejection based on the alleged requirement for having computer implementation, such as the rejection above requiring performance of a computer-implemented task.

Therefore, in light of any of the applicable Federal case law precedent or the Office's own guidelines, the claimed production of an altered model having improved predictive capabilities of an organism's metabolic network of claims 1-8, 10-15, 19-27, 29-31 and 33 satisfy the requirements of § 101 for statutory patentable subject matter. Thus, withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-16, 19-22 and 29-33 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. The Office asserts that the phrase "tighten the boundaries for available flux distribution" and the phrase "tighten the stoichiometric boundaries" lack support allegedly because "tighten" refers to increasing the accuracy of a model which is distinct from tightening stoichiometric boundaries or boundaries for flux distributions, and because the phrase "stoichiometric boundaries" is not found in the application, respectively.

To meet the written description requirement the language of the specification must describe the claimed invention so that one skilled in the art can recognize what is claimed. *Enzo Biochem, Inc., v. Gen-Probe Inc.*, 296 F.3d 1316, 1328 (Fed. Cir. 2002). Applicants have met this well established standard. The application describes with sufficient clarity each of the rejected elements of the claimed invention such that one skilled in the art can recognize the full scope of the invention as claimed. Such description demonstrates not only that Applicants contemplated the invention, but also shows that Applicants were in possession of the claimed invention at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

Briefly, with respect to the phrase "stoichiometric boundaries" alleged by the Office to not be disclosed anywhere in the instant specification, Applicants respectfully point to page 3, lines 1-2, where the application describes:

> The key disadvantage is that the obtained stoichiometric boundaries can be very wide and it is hard to envision that the biomass maximization conjecture, while useful under certain conditions, is generally applicable.

Emphasis added.

Accordingly, the application expressly recites the rejected element and removal of this ground of rejection is respectfully requested.

With respect to the elements directed to tightening the boundaries for available flux distribution and to tightening the stoichiometric boundaries, Applicants respectfully disagree that these elements lack support because one skilled in the art would recognize what is claimed after reading the entire application. Nevertheless, these phrases have been amended and this ground of rejection is moot. To the extent any of the amended phrases utilize words in the rejected elements, Applicants draw the Office's attention to the support cited previous (see, for example, page 8, para. 1, *supra*). Therefore, withdrawal of this ground of rejection is respectfully requested.

Claims 2 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, for lacking written description allegedly because the phrase "at least a subset" of logic constraints lacks support in the specification.

Applicants respectfully draw the Office's attention to the section entitled "Modeling and Computational Protocol" at pages 54-58 of the application which sets forth the use, *inter alia*, of connectivity constraints. The application teaches partitioning, for example, a reaction set into two subsets and expression of this subset partitioning as connectivity constraints when it describes:

> Connectivity constraints are also added to ensure that if a reaction producing an intracellular metabolite is active, then at least one reaction consuming this metabolite must be active and vice versa. In addition, if a reaction transporting an extracellular metabolite into the cell is active, then at least one intracellular reaction consuming this metabolite must be active and vice versa. These relations are incorporated in the model as follows after partitioning the reaction set J into two subsets: J_{int} representing intracellular reactions and J_{trans} representing reactions transporting metabolites to and from the cell. The metabolite set I is

> also partitioned into two subsets with I_{int} and I_{ext} representing intracellular and extracellular metabolites respectively.
>
> ****
>
> These connectivity constraints are also employed to identify the smallest set of reactions capable of ensuring adequate connectivity between the external metabolites and the components of biomass.

Application at page 57, para. 3 through page 58, para. 1 (emphasis added; formulas omitted).

Accordingly, the application sufficiently supports the rejected phase such that one skilled in the art would recognize what is claimed after reading the entire application. Withdrawal of this ground of rejection is respectfully requested.

Claim 22 stands rejected under 35 U.S.C. § 112, first paragraph, for lacking written description allegedly because the phrase "DNA experimental data constraints" lack support in the application. The Office acknowledges that the phrase "differential DNA microarray experimental data constraints" is supported in the application, but alleges that the rejected phrase is not derived from the acknowledged phrase and is not recited or disclosed in the specification.

Applicants respectfully disagree. The application describes:

> These constraints incorporate, without limitation, qualitative kinetic information, qualitative regulatory information, and/or DNA microarray experimental data. Preferably, these constraints are logic constraints . . .

Application, paragraph bridging pages 7-8 (emphasis added).

Accordingly, the application sufficiently supports the rejected phase such that one skilled in the art would recognize what is claimed after reading the entire application. Withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-16, 19-27 and 29-33 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because the phrase "modeling cellular metabolism of an organism" in the preamble of independent claims 1, 6, 19, 23, 29, 30 and 33 is unclear. The Office alleges that the steps of the claims fail to recite any relationship of an FBA model to an organism and therefore, unclear with respect to the preamble.

Although clear as written, independent claims 1, 6, 19, 23, 29, 30 and 33 have been amended to recite that a flux balance analysis model for a metabolic network is constructed. Accordingly, the claim explicitly recite the relationship between the preamble and the steps of the method because it is the construction of the flux balance analysis model of an organism's metabolic network which produces the model. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 4, 14, 26, 27, 30 and 31 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it is unclear to what the mixed integer linear programming is applied.

Applicants respectfully point out that claims 27 and 31 do not recite the rejected element. Although clear as written, claims 14, 26 and 30 have been amended to explicitly recite that the mixed integer linear programming is applied to the flux balance analysis model having improved predictive capabilities. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 4, 5, 14, 26, 27, 30 and 31 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because the phrase "to solve for a desired metabolic

outcome" it is unclear as to what is being solved. The Office alleges that the claims neither recited any equations to be solved or what is intended as a solution of the model.

The requirement for precision in claiming is satisfied if a person skilled in the field of the invention would reasonably understand the claim when read in the context of the specification. *Marley Moldings Limited v. Mikron Industries, Inc.*, Case No.04-1441, slip op. at 5 (Fed. Cir. August 8, 2005) *citing Union Pac. Res. Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 692 (Fed. Cir. 2001) (the definiteness requirement of §112, second paragraph "focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification"). The phrase "to solve for a desired metabolic outcome" when read in light of the specification reasonably apprises those skilled in the art of the scope of the claim.

The application teaches throughout the meaning and use of applying mixed-integer linear programming to a flux balance analysis model to solve for a desired metabolic outcome. For example, the application teaches:

> The modeling framework of the present invention further provides for computational procedures to be used to solve the network problems presented. The computational procedures to be used include mixed-integer linear programming techniques.
>
> The algorithmic frameworks of the present invention in the context of gene addition, regulation, DNA array data superposition, genetic circuit elucidation and minimal reaction set identification inherently require the use of discrete optimization variables that give rise to MILP problems. . . .
>
> The key source of complexity in MILP problems in metabolic networks is the number of reactions/genes whose on or off switching as well as prediction of over- or under-expression requires binary 0-1 variables to describe. These problems belong to the class of generalized network problems where each metabolite constitutes a node and each reaction represents an arc in the network. Given that existing FBA models for prokaryotes contain hundreds of reactions and upcoming models for *S. cerevisiae* willikely be in the thousands motivates the need to harness complexity. In addition, the tremendous redundancy, redirection capability and multiplicity of steady-state solutions further exasperates complexity issues.

Id. at page 25, para. 1-3 (emphasis added; citations omitted).

The application further teaches at, for example, pages 25-27, mathematical techniques to apply mixed-integer linear programming to the flux balance analysis models to solve the linear programming problem of flux balance analysis models. Additionally, the Examples further exemplify at, for example, pages 27-45 and at pages 45-59, the application of mixed-integer linear programming to flux balance analysis models to solve for the metabolic outcome of the model or to solve for a desired metabolic outcome in light of gene additions, deletions and/or other perturbations. Application of mixed-integer linear programming to select for mathematically optimal genes is taught at, for example, page 18, first paragraph, and the integration of mixed-integer linear programming and logic constraints to tighten obtained predictions of a flux balance analysis model is exemplified at, for example, page 20, last paragraph.

In light of these exemplary teachings, Applicants submit that the objected phrase is sufficiently clear and would be understood by one skilled in the art when read in the context of the application to refer to use of mixed-integer linear programming problems to a flux balance analysis model to solve for the model's metabolic capabilities or output under the set of conditions used to construct or modify the model. Therefore, the term is sufficiently clear to satisfy the requirements of the second paragraph of § 112 and withdrawal of this ground of rejection is respectfully requested.

Claim 16 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because the phrase "the change" lacks antecedent support. Claim 16 has been amended to correct this informality and now recites "a change." Accordingly, this ground of rejection is moot and its withdrawal is respectfully requested.

Claims 16 and 32 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because the phrase "an organism" is unclear as to whether it refers to the same organism recited in base claims 6 and 30. Further, claims 16 and 32 also stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because the phrase "based on" is unclear with respect to the relationship between the recited engineered change and the desired metabolic outcome.

Applicants submit that the term is clear as written. Base claims 6 and 30 recite "a method for modeling cellular metabolism of an organism" and do not refer directly to an organism. In comparison, claims 16 and 32 recited engineering a change in an organism. The engineered change is based on the desired metabolic outcome of the model. Accordingly, when read in light of the application and respective base claims, one skilled in the art would understand this term to refer to an actual organism and not to the model of their base claims. The claims therefore satisfy the precision requirement of the second paragraph of § 112 and withdrawal of this ground of rejection is respectfully requested.

Claim 30 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because the phrase "associated with" is unclear with respect to the relationship between the recited metabolic outcome and the organism.

Although clear as written, claim 30 has been amended to recite improved predictive capabilities for a desired metabolic outcome of the flux balance analysis model of the organism. As described previous with respect to claims 4, 5, 14, 26, 27, 30 and 31, mixed-integer linear programming can be used in conjunction with flux balance analysis models to solve for the model's capabilities or a desired outcome under given conditions. Accordingly, the amendment renders this ground of rejection moot and its withdrawal is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1-8, 12-15, 19, 22-23, 25-27 and 29-33 stand rejected under 35 U.S.C. § 102 for allegedly being anticipated by Palsson et al., US 2002/0012939. The Office alleges that Palsson describes applying constraints to stoichiometric mass balances that results in a restricted model of cellular metabolism. The constrains allegedly include those for maintenance of kinetic requirements or connectivity constraints and relate reaction fluxes and metabolic concentrations of analytes.

When lack of novelty is based on a printed publication that is asserted to describe the same invention, a finding of anticipation requires that the publication describe all of the elements of the claims. *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1349, 48 U.S.P.Q.2d 1225, (Fed. Cir. 1998) (quoting *Shearing v. Iolab Corp.*, 975 F.2d 1541, 1544-45, 24 U.S.P.Q.2d 1133, 1136 (Fed. Cir. 1992)). The Office has failed to establish a *prima facie* case of anticipation because Palsson et al. does not teach logic constraints as described and claimed by the invention.

The invention is directed to a method for modeling cellular metabolism of an organism that includes constructing a flux balance analysis model and applying logic constraints to constrain a boundary for an available flux distribution. The claimed logic constraints are distinguished in the application from other constraints placed on flux balance models because they tighten the predicted stoichiometric flux boundaries arrived at by flux balance analysis models. Palsson et al. describes, at most, flux balance analysis models. For example, Palsson et al. describes:

> This invention relates to constructing metabolic genotypes and genome specific stoichiometric matrices from genome annotation data. The functions of the metabolic genes in the target organism are determined by homology searches

against databases of genes from similar organisms. Once a potential function is assigned to each metabolic gene of the target organism, the resulting data is analyzed. In one embodiment, each gene is subjected to a flux-balance analysis to assess the effects of genetic deletions on the ability of the target organism to produce essential biomolecules necessary for its growth.

*****

Construction of a genome-specific stoichiometric matrix from genomic annotation data is illustrated along with applying flux-balance analysis to study the properties of the stoichiometric matrix, and hence the metabolic genotype of the organism. By limiting the constraints on various fluxes and altering the environmental inputs to the metabolic network, genetic deletions may be analyzed for their affects on growth.

Palsson et al. at para. [0016]-[0018] (emphasis added).

Therefore, according to Palsson et al., this publication describes application of flux balance analysis using stoichiometric matrices and placing limitations and alterations on the constraints and inputs used in the analysis. There is no description of logic constraints as described and claimed by the invention.

Further, the constraints for flux balance analysis described by Palsson et al. are set by the user to limit the value of a flux in the flux balance analysis. For example, Palsson et al. describes:

Applying equation 1 to our system we let S now represent the genome specific stoichiometric matrix.

To determine the metabolic capabilities of a defined metabolic genotype Equation 1 is solved for the metabolic fluxes and the internal metabolic reactions, v, while imposing constraints on the activity of these fluxes. . . . The solutions to Equation 1 lie in a restricted region. This subspace defines the capabilities of the metabolic genotype of a given organism, since the allowable solutions that satisfy Equation 1 and any constraints placed on the fluxes of the system define all the metabolic flux distributions that can be achieved with a particular set of metabolic genes. *****

Objectives for metabolic function can be chosen to explore the 'best' use of the metabolic network within a given metabolic genotype. The solution to equation 1

can be formulated as a linear programming problem, in which the flux distribution that minimizes a particular objective [is] found. *****

This general representation of Z enables the formulation of a number of diverse objectives. These objectives can be design objectives for a strain, exploitation of the metabolic capabilities of a genotype, or physiologically meaningful objective functions, such as maximum cellular growth. For this application, growth is to be defined in terms of biosynthetic requirements based on literature values of biomass composition or experimentally determined values such as those obtained from state 60. Thus, we can define biomass generation as an additional reaction flux draining intermediate metabolites in the appropriate ratios and represented as an objective function Z. . . . This new reaction flux then becomes another constraint/balance equation that the system must satisfy as the objective function. . . . Setting this new flux as the objective function and asking the system to maximize the value of this flux for a given set of constraints on all the other fluxes is then a method to simulate the growth of the organism.

Using linear programming, additional constraints can be placed on the value of any of the fluxes in the metabolic network. *****

These constraints could be representative of a maximum allowable flux through a given reaction, possibly resulting from a limited amount of an enzyme present in which case the value for α_j would take on a finite value. These constraints could also be used to include the knowledge of the minimum flux through a certain metabolic reaction in which case the value for β_j would take on a finite value. Additionally, if one chooses to leave certain reversible reactions or transport fluxes to operate in a forward and reverse manner the flux may remain unconstrained by setting β_j to negative infinity and α_j to positive infinity. If reactions proceed only in the forward [direction] β_j is set to zero while α_j is set to positive infinity. As an example, to simulate the event of a genetic deletion the flux through all of the corresponding metabolic reactions related to the gene in question are reduced to zero by setting β_j and α_j to be zero in Equation 4. Based on the *in vivo* environment where the bacteria lives one can determine the metabolic resources available to the cell for biosynthesis of essentially molecules for biomass. Allowing the corresponding transport fluxes to be active provides the *in silico* bacteria with inputs and outputs for substrates and by-products produces by the metabolic network. Therefore as an example, if one wished to simulate the absence of a particular growth substrate one simply constrains the corresponding transport fluxes allowing the metabolite to enter the cell to be zero by allowing β_j and α_j to be zero in Equation 4. On the other hand if a substrate is only allowed to enter or exit the cell via transport mechanisms, the corresponding fluxes can be properly con strained to reflect this scenario.

Palsson et al. at para. [0039]-[0045] (emphasis added).

As set forth in the above paragraphs relied on by the Office for describing Applicants' claimed logic constraints, the constraints described by Palsson et al. are values imposed as a solution to a linear equation. These values are selected and applied by the user to limit particular fluxes or the objective function of the flux balance analysis. Therefore, Palsson et al. does no more than describe flux balance analysis and setting constraints for biasing fluxes to a desired value in order to represent a maximum or minimum allowable flux or in order to make the value a requirement a requirement for satisfying the objective function. Accordingly, Palsson et al. does not describe logic constrains as described and claimed by the invention.

In contrast, the application teaches that flux balance models relying solely on stoichiometric balances and uptake rates lead to overly optimistic expectations and that the predictive capabilities can be improved by inclusion of logic constraints to ensure consistency of between the flux balance analysis and the kinetic and regulatory loops of the network. For example, the application teaches:

> Flux balance models, by relying solely on stoichiometric balances and uptake rates are guaranteed not to exclude any feasible flux distributions. However, this versatility may lead to overly optimistic expectations if the results are not interpreted properly. The flux distributions within the cell are ultimately uniquely determined by the regulatory mechanisms within the cell, the kinetic characteristics of cellular enzymes, and the expression of these enzymes. Assuming cells operate in a stoichiometrically optimal fashion may yield metabolic flux distributions not available to the cell. The present invention provides for multiple methods for tightening the predicted stoichiometric flux boundaries by FBA models. A first strategy involves attempting to ensure that flux changes identified through FBA are consistent, in a qualitative sense, with the kinetics and regulatory loops of the metabolic network. By uncovering unreachable domains within the stoichiometric flux boundaries the predictive capabilities are improved.

Application at page 10, para. 2 through page 11, line 3 (emphasis added).

The application further teaches that a regulatory matrix is imposed on the analysis using logic constraints that determine whether the optimal flux distributions predicted by flux balance analysis will be prohibited. For example, the application teaches:

> The key question addressed here is whether the optimal flux distributions predicted by the FBA models are reachable by the cell or whether kinetic and/or regulatory boundaries will prohibit the system from reaching the stoichiometric boundaries (see Figure 4).
>
> The key idea we propose to explore is to ensure, by using logic relations, that when in response to environmental changes, the metabolic network shifts from one steady-state to another, up or down changes in metabolite concentrations are consistent with up or down changes in reaction fluxes.

Id. at page 11, para. 1-2 (emphasis added).

The application at page 11, paragraph 3 through the paragraph bridging pages 12-13 further teaches that logic constraints incorporated into a flux balance analysis framework requires a regulation matrix F to be established that describes the effects of a metabolite on a reaction for each metabolite *i* and each reaction *j*. Exemplary logic constrains incorporated into a flux balance model which maintain consistency with the kinetic and regulatory barriers are shown in Equations 1-3 (page 12). As described therein, these constraints yield the equations set forth in the first paragraph of page 13. Such logic constraints are distinct from the values described by Palsson et al. to limit fluxes in a flux balance analysis.

Palsson et al. describe actually setting values for fluxes to bias a reaction toward a in order to represent a maximum or minimum allowable flux or in order to make the value a requirement a requirement for satisfying the objective function. Palsson et al. nether describe the use of kinetic and regulatory boundaries in combination with flux balance analysis to determine whether they prohibit the stoichiometric boundaries nor does Palsson et al. describe incorporating the claimed logic constraints through, for example, a regulation matrix F. Palsson et al. also fail

to describe that flux balance analysis can lead to overly optimistic expectations and therefore, cannot describe constraints that tighten the predicted stoichiometric flux boundaries as claimed.

Because the invention claims applying logic constraints to tighten the boundaries for available flux distributions and Palsson et al. fails to describe such logic constraints, Palsson et al. cannot anticipate the claimed invention. Therefore, withdraw of this ground of rejection is respectfully requested.

CONCLUSION

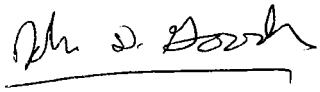
In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

This is a request under the provision of 37 CFR § 1.136(a) to extend the period for filing a response in the above-identified application for two months from December 28, 2006 to February 28, 2007. Applicant is a small entity; therefore, please charge Deposit Account number 26-0084 in the amount of $225.00 to cover the cost of the two-month extension. Any deficiency or overpayment should be charged or credited to Deposit Account 26-0084.

No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



JOHN D. GOODHUE, Reg. No. 47,603
McKEE, VOORHEES & SEASE, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No: (515) 288-3667
Fax No: (515) 288-1338
CUSTOMER NO: 27407

Attorneys of Record

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